IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Aomatsu et al.	EXAMINER:	Tran, My Chau T
SERIAL NO.:	09/674,819	ART UNIT:	1639
FILED:	11/06/2000	CONFIRMATION NO.:	5038
FOR:	GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME		

APPEAL BRIEF TO THE BOARD OF PATENT APPEALS AND INTERFERENCES, PURSUANT TO 37 CFR § 41.37

Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This Brief on Appeal to the Board of Patent Appeals and Interferences is submitted, under 37 CFR §41.37 on behalf of the Applicants, in appeal of a Final Office Action mailed November 1, 2006, and subsequent Advisory Action dated February 7, 2007. The Notice of Appeal was filed on March 5, 2007, making the Appeal Brief due on or before Saturday May 5, 2007. Applicant is mailing this appeal brief on Friday May 4, 2007. Therefore, the present Appeal Brief is being timely filed.

The Commissioner is authorized to charge the $500.00 Appeal Brief fee (37 CFR §41.20(b)(2)) to Deposit Account 16-1445. If additional charges are required with the filing of this Brief, Applicant authorizes the Commissioner to charge the fee to the same deposit account.

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(1) Real Party in Interest

The real party in interest of the above-referenced application is Pfizer Inc a U.S. Corporation organized under the laws of the State of Delaware and having its headquarters at 235 East 42nd Street, New York, New York, by virtue of assignment from the inventor to the Warner-Lambert Company dated April 2, 1999 and recorded in the U.S. Patent and Trademark Office on April 22, 1999 at reel number 9907 and frame number 0229. Assignee Warner-Lambert Company is a wholly owned subsidiary of Pfizer Inc.

(2) Related Appeals and Interferences

There are no other appeals or interferences presently pending for application 09/674,819 which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant pending appeal.

(3) Status of the Claims

Claims 28, 35-37, 40, 41, and 43 were rejected in the Final Office Action mailed November 1, 2006 and subsequent Advisory Action mailed February 7, 2007. Claims 28 and 41 are independent claims. Claims 28, 35-37, 40, 41, and 43 are pending in this appeal. The appealed claim set is provided in the Claims Appendix of this paper.

(4) Status of Amendments

Applicant submitted an after file amendment on December 20, 2006, wherein Applicant amended independent claims 28 and 41 by deleting the term "or a combination thereof". An Advisory Action mailed February 7, 2007 informed Applicant that the claim amendments filed December 20, 2007 would be entered for purposes of appeal and that claims 28, 35-37, 40, 41, and 43 were rejected for reasons set forth on pages 3-7 of the Final Office Action mailed November 1, 2006.

(5) Summary of Claimed Subject Matter

Independent claim 28 of the present invention is drawn to a stabilized solid composition comprising a 4-amino-3-substituted butanoic acid derivative (PCT/US99/10186, page 1, lines 5-7) and propylene glycol (PCT/US99/10186, page 41, line 15), wherein the butanoic acid derivative is gabapentin or pregabalin (PCT/US99/10186, page 1, line 15), for the manufacture of a pharmaceutical preparation (PCT/US99/10186, page 1, line 13). Claims 35-37 and 40 depend from claim 28. Claim 41 is drawn to a process for stabilizing a solid composition containing a 4-amino-3-substituted butanoic acid derivative (PCT/US99/10186, page 21, lines 12), wherein the butanoic acid derivative is gabapentin or pregabalin (PCT/US99/10186, page 41, line 41) combined with propylene glycol (PCT/US99/10186, page 41, line 15). Claim 43 depends from claim 41. Compositions of the present invention exhibit significantly improved physical stability during storage, as manifested by a reduced tendency of the drug to form a lactam impurity.

(6) **Grounds of Rejection to be Reviewed on Appeal**

The issues on appeal are (a) whether the composition of claims 28, 36, 40, and 41 are anticipated by Schrier et al. (WO 98/58641, hereinafter "Schrier", Exhibit A) under 35 U.S.C. §102(a); (b) whether claims 28 and 43 are anticipated by Schrier under 35 U.S.C. §102(a), or in the alternative, unpatentable under 35 U.S.C. §103(a) as being obvious in view of Schrier; and (c) whether claims 28, 35-37, 40, and 41 are obvious under 35 U.S.C. §103(a) in view of Schrier.

(7) Argument

Claims 28, 35-37, 40, 41, and 43 stand rejected as of the Final Office Action mailed November 1, 2006 and an Advisory Action dated February 7, 2007. A Notice of Appeal was received March 5, 2007. Applicant submits the following arguments to overcome the Office's final rejection.

a) Rejection of claims 28, 36, 40, and 41 under 35 USC §102(a).

The Final Office Action and subsequent Advisory Action rejected claims 28, 36, 40, and 41 under 35 U.S.C. §102(a) as being anticipated by Schrier et al. (WO 98/58,641, hereinafter Schrier, Exhibit A). Applicant respectfully submits that Schrier does not qualify as prior art under §102(a) and therefore cannot anticipate the present invention. According to the Patent Act:

> "A person shall be entitled to a patent unless the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for patent."

35 U.S.C. §102(a). Thus, to anticipate an invention, a reference must be known or used in this country or described in a printed publication before the instant invention. The statutory language "known or used" by others in this country means knowledge or use which is accessible to the public if there has been no deliberate attempt to keep it secret. *Carella v Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986). Schrier did not publish until December 30, 1998 (Exhibit A) and was therefore inaccessible to the public prior to that date. Furthermore, Schrier's publication date is later than the priority date of the present invention, May 21, 1998, which is the filing date of US Provisional application number 60/086,269 (Exhibit B and C). Therefore, Applicant respectfully requests that the §102(a) rejection be withdrawn and the claims be allowed to issue.

Further, Schrier does not qualify as prior art under §102(e). Schrier has an international filing date of June 24,1998 and an international publication date of December 30, 1998. Pursuant to section 13205 of Public Law 107-273, an international application filed before November 29, 2000 shall not be effective as prior art as of the filing date of the international application. Further, the cover page of US 6,329,429B1 (Exhibit D) which issued from the Schrier reference provides a calculated §102(e) date of October 25, 1999, which is after the priority date (May 21, 1998) of the present application.

Even if Schrier did qualify as prior art against the present invention, Applicant submits that none of claims 28, 36, 40, and 41 would be anticipated by Schrier because the reference fails to disclose every limitation claimed in the instant application. Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475; USPQ2d 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic and Res. Found. v Genentech, Inc.*, 927 F.2d 1565; 18 USPQ2d 1001 (Fed.Cir. 1991) The corollary of the rule is that absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v Crucible Inc.*, 848 F.2d 1565; 230 USPQ 81 (Fed. Cir. 1986). This invention provides a stabilized solid composition characterized by the addition of a humectant, propylene glycol, to gabapentin or pregabalin. In contrast, Schrier does not teach the use of propylene glycol to stabilize gabapentin or pregabalin.

Applicant has shown that the addition of propylene glycol significantly reduces the amount of lactam formation (lactamization) of gabapentin and pregabalin following various storage conditions. In contrast, Schrier provides a general listing of common formulation excipients used in manufacturing multiple dosage forms. Schrier does not provide a single example that shows a stabilized pharmaceutical composition containing propylene glycol and gabapentin or pregabalin. Instead, Schrier exemplifies liquid solutions and suspensions of gabapentin and pregabalin in a vehicle of hydroxypropyl-methylcellulose and Tween80 and an injectible formulation in an artificial cerebral spinal fluid. In view of this, Applicant respectfully submits that Schrier does not anticipate the pending claims of the instant invention.

b) Rejection of claims 28 and 43 under 35 USC §102(a), or in the alternative under §103(a)

The office rejected claims 28 and 43 under 35 USC §102(a) as being anticipated by Schrier, or in the alternative, under 35 USC §103 as obvious over Schrier. Applicant submits that Schrier cannot be used as §102 art against Applicant for reasons discussed above. Since Schrier is not prior art under §102, it cannot be considered prior art under §103. Compare *Ex Parte Andersen*, 212 USPQ 100, 102 (Bd. Pat. App. & Inter. 1981), MPEP 2141.01 (I), wherein the Board held that subject matter that is prior art under §102 can be used to support a rejection under §103. Applicant respectfully submits that Schrier is improper art under §103 and cannot sustain the Office's rejection of the present claims.

Even if Schrier did qualify as prior art against the present invention, the Examiner has failed to establish a prime facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to a skilled artisan, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed Cir. 1991).

As described, Schrier provides a general listing of suitable pharmaceutical carriers, glidants, and diluents including sugars, starches, cellulose derivatives, gelatin, talc, glidants, vegetable oils, glycerin, glycols, water, buffer solutions and other compatible substances normally used in preparing pharmaceutical formulations. However, Schrier does not provide any indication that the broad list of suitable excipients could in and of themselves prevent lactamization of gabapentin or pregabalin. At most, Schrier only represents an "obvious to try rationale," which cannot render the claims

obvious. *In re Geiger*, 815 F.2d at 688, 2 USPQ2d at 1278; *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed Cir 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 90-91 (Fed. Cir. 1986) – cert. denied 107 S.Ct. 1606, 94 L.Ed.2d. 792 (1987). Applicant submits that Schrier provides numerous choices of pharmaceutical excipients for the manufacture of a pharmaceutical formulation. However, Schrier does not provide any guidance for determining whether any particular excipient will provide stability of the drug product during manufacture and/or storage of the finished product. As such, there is no teaching or suggestion or reasonable expectation of success provided by Schrier to manufacture a stable solid dosage form wherein the humectant, polypropylene glycol, prevents lactam formation. Further, Schrier does not teach or suggest all of the claim limitations of the present invention.

Notwithstanding the Examiner's failure to establish such a prime facie case, Applicant has demonstrated that the stabilizing effects taught and claimed in the instant application are unanticipated and unobvious.

(c) Rejection of claims 28, 35-37, 40, and 41 under §103(a).

The office rejected claims 28, 35-37, 40, and 41 under 35 USC §103(a) as being unpatentable in view of Schrier. For the reasons set forth above, Applicant respectfully submits that the present invention is patentable over Schrier.

d) Conclusion

Applicant respectfully requests that the finality of the §102(a) and §103(a) rejections be withdrawn and that the claims of the present invention be allowed to issue.

(8) Claims Appendix

Claims 1-27 (canceled).

Claim 28 (Previously presented): A stabilized solid composition comprising a 4-amino-3-substituted butanoic acid derivative and propylene glycol, wherein the 4-amino-3-substituted butanoic acid derivative is gabapentin or pregabalin.

Claims 29-34 (canceled).

Claim 35 (previously presented): The stabilized solid composition of claim 28, wherein the amount of the propylene glycol is 0.01-25 % by weight relative to the 4-amino-3-substituted butanoic acid derivative.

Claim 36 (previously presented): The stabilized solid composition of claim 28, further comprising an auxiliary agent.

Claim 37 (previously presented): The stabilized solid composition of claim 36, wherein the total amount of the propylene glycol is 0.01-25 % by weight relative to the 4-amino-3-substituted butanoic acid derivative and the auxiliary agent.

Claims 38-39 (canceled).

Claim 40 (previously presented): The stabilized solid composition of claim 28, wherein the stabilized solid composition is a pharmaceutical preparation in the form of tablets, granules or capsules.

Claim 41 (Previously presented): A process for stabilizing a solid composition containing a 4-amino-3-substituted butanoic acid derivative, the process comprising combining the 4-amino-3-substituted butanoic acid derivative with propylene glycol, wherein the 4-amino-3-substituted butanoic acid derivative is gabapentin or pregabalin.

Claim 42 (canceled).

Claim 43 (Previously presented): The stabilized solid composition of claim 28, wherein after storage of the composition in a sealed container at 60°C for 2 weeks the content of the corresponding lactam that is formed in the composition is less than 0.20% by weight relative to the initial amount of the 4-amino-3-substituted-butanoic acid derivative in the composition.

(9) Evidence Appendix

a) Exhibit A - WO 98/58641 (Schrier et al.)

b) Exhibit B – Inventor assignment and filing dates

c) Exhibit C - §371 Confirmation

d) Exhibit D – US 6,329,429 face sheet

(10) Related Proceedings Appendix

No related proceedings documents are enclosed for reasons set forth in (2) above.

Respectfully submitted,

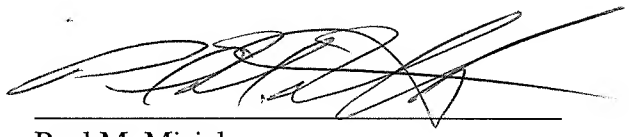

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Exhibit A

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/195 — A1

(11) International Publication Number: **WO 98/58641**

(43) International Publication Date: 30 December 1998 (30.12.98)

(21) International Application Number: PCT/US98/13107

(22) International Filing Date: 24 June 1998 (24.06.98)

(30) Priority Data:

60/050,736	25 June 1997 (25.06.97)	US
60/084,183	4 May 1998 (04.05.98)	US

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(81) Designated States: AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF GABA ANALOGS SUCH AS GABAPENTIN IN THE MANUFACTURE OF A MEDICAMENT FOR TREATING INFLAMMATORY DISEASES

(57) Abstract

GABA analogs such as gabapentin and pregabalin are useful to prevent and treat inflammatory diseases.

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Use of Gaba analogs such as Gabapentin in the manufacture of a medicament for treating inflammatory diseases

This invention was made in part with United States Government support under Grant No. IR01NS32778-01A1 administered by the National Institute of Health. The Federal Government may own certain rights in the invention.

FIELD OF THE INVENTION

This invention relates to a method for treating inflammatory diseases by administering a gamma-aminobutyric acid (GABA) analog.

BACKGROUND OF THE INVENTION

Inflammatory diseases are characterized by a complex series of histological events, including dilatation of arterioles, capillaries, and venules, with increased permeability and blood flow; exudation of fluids, including plasma proteins; and leukocytic migration into the inflammatory focus. Many forms of inflammation are localized protective responses elicited by injury or destruction of tissues, which serves to destroy, dilute, or wall off both the injurious agent and the injured tissue. The inflammatory response itself is also responsible for pathologic tissue damage. Arthritis is a particularly devastating inflammatory disease, generally affecting older people, and is characterized by the inflammatory lesions being primarily confined to articular joints. The disease is marked by pain, heat, redness, swelling, and tissue destruction. Rheumatoid arthritis is a chronic systemic disease of the joints, marked by inflammatory changes in the synovial tissue and articular structures, and by atrophy and rarefaction of the bones. This form of inflammatory disease generally progresses to deformity and ankylosis.

Numerous anti-inflammatory treatments are known and commonly used. The most common are the nonsteroidal anti-inflammatory agents such as naproxen, diflunisal, mefenamic acid, and ketorolac tromethamine. These agents generally are used to treat short term mild inflammation and pain. More severe

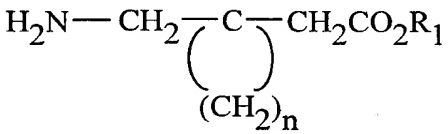
inflammatory disease, such as arthritis, are treated with steroidal hormones and glucocorticoids, for example prednisolone, hydrocortisone acetate, and betamethasone sodium phosphate.

Because many of the anti-inflammatory agents are only short acting, and often produce severe side effects, the need for new therapies continue. We have now discovered that compounds which are analogs of gamma aminobutyric acid (GABA) are useful to treat inflammatory diseases. All that is required to prevent or treat the inflammatory disease according to this invention is to administer to a subject in need of treatment an anti-inflammatory amount of a GABA analog.

Several GABA analogs are known. Gabapentin, a cyclic GABA analog, is now commercially available and extensively used clinically for treatment of epilepsy and neuropathic pain. Such compounds are described in U.S. Patent 4,024,175. Another series of GABA analogs is described in U.S. Patent 5,563,175.

SUMMARY OF THE INVENTION

This invention provides a method for preventing and treating inflammatory diseases comprising administering to a subject suffering from such disease or suspected of developing such disease and in need of treatment an effective amount of a GABA analog. A preferred embodiment utilizes a cyclic amino acid compound of Formula I

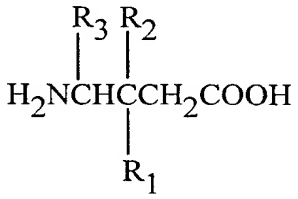


I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 5, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as

gabapentin. Other preferred GABA analogs have Formula I wherein the cyclic ring is substituted, for example with alkyl such as methyl or ethyl. Typical of such compounds include (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl) acetic acid, and (1-aminomethyl-3,4-dimethylcyclopentyl) acetic acid.

In another embodiment, the anti-inflammatory method of the invention utilizes a GABA analog of Formula II



II

or a pharmaceutically acceptable salt thereof, wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl.

Diastereomers and enantiomers of compounds of Formula II can be utilized in the invention.

An especially preferred method of the invention employs a compound where R_2 and R_3 are both hydrogen, and R_1 is $-(CH_2)_{0-2}$-i C_4H_9 as an (R), (S), or (R,S) isomer.

A more preferred embodiment of the invention utilizes 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-(aminomethyl)-5-methylhexanoic acid, now known generically as pregabalin. Pregabalin is also known as "CI-1008" and "S-(+)-3-IBG." Another preferred compound of Formula II is 3-(1-aminoethyl)-5-methylhepanoic acid.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the method of this invention utilizes any GABA analog. A GABA analog is any compound derived from or based upon gamma-aminobutyric acid, and causes an anti-inflammatory effect in accordance with this invention. The compounds are readily available, either commercially, or by synthetic methodology well-known to those skilled in the art of organic chemistry. The preferred GABA analogs to be utilized in the method of this invention are cyclic amino acids of Formula I. These are described in U.S. Patent 4,024,175 which is incorporated herein by reference. Another preferred method utilizes the GABA analogs of Formula II, and these are described in U.S. Patent 5,563,175 which is incorporated herein by reference.

All that is required to practice the anti-inflammatory method of this invention is to administer a GABA analog in an amount that is effective to prevent or treat the inflammatory condition. Such anti-inflammatory amount will generally be from about 1 to about 300 mg per kg of subject body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult subject of normal weight.

Pharmaceutical compositions of a GABA analog or its salts are produced by formulating the active compound in dosage unit form with a pharmaceutical carrier. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses. Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions to be employed in the invention

can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents commonly employed to treat inflammation, for example, aspirin, naprosyn, and similar anti-inflammatory agents.

The percentage of the active ingredients in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present, for example, up to about 95%.

Routes of administration of the GABA analog or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg, and a useful oral dosage is between 20 and 800 mg. The dosage is within the dosing range used in treatment of inflammatory diseases such as arthritis, or as would be determined by the needs of the patient as described by the physician.

A unit dosage form of the GABA analog to be used in this invention may also comprise other compounds useful in the therapy of inflammatory diseases.

The advantages of using the compounds of Formula I and II, especially gabapentin and pregabalin, in the instant invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are well-tolerated, and the ease of IV and oral administration of the drugs. Further, the drugs are not metabolized in the body.

The subjects as used herein are mammals, including humans.

The ability of GABA analogs to treat inflammatory diseases according to this invention has been established in several animal models of inflammation and arthritis.

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows the effects of pregabalin (designated as S-(+)-3-IBG), its corresponding R optical enantiomer R-(-)-3-isobutyl GABA (designated as R-(-)-3-IBG), and aCSF (artificial cerebrospinal fluid) on thermal PWL (paw withdrawal latency), on circumference of the knee joint, and on degree of pain in animals prior to development of acute arthritis.

Figure 2 shows the effects of 0.9 and 10 mg/mL doses of pregabalin, R-(-)-3-IBG, and aCSF on thermal paw withdrawal latencies, administered after development of acute arthritis.

Figure 3 shows the effects of 0.9 and 10 mg/mL of Pregabalin, R-(-)-3-IBG and aCSF on joint swelling, administered after development of acute arthritis.

Figure 4 shows the effects of 0.9 and 10 mg/mL of pregabalin, R-(-)-3-IBG and aCSF on pain-related behavior, when administered after development of acute arthritis.

The following detailed examples illustrate the specific anti-inflammatory activity of GABA analogs.

EXAMPLE 1

Gabapentin was evaluated in a streptococcal cell wall (SCW)-induced paw edema model. Female Lewis rats were sensitized to SCW (6 μg/rat) in the right tibiotalar joint on Day 0. Vehicle (0.5% hydroxypropylmethylcellulose/0.2% Tween 80) or drug (100 mg/kg, BID) was administered orally (10 mL/kg) beginning 1 hour before initiation of the delayed-type hypersensitivity reaction by systemic SCW (100 μg/rat) on Day 21, and given through Day 24. Assessment of hindpaw edema was determined on Days 22 through 25 by mercury plethysmometry.

Gabapentin was found to significantly inhibit swelling on Days 22, 23, 24, and 25 (58%, 77%, 83%, and 81%, respectively).

EXAMPLE 2

Pregabalin was evaluated in a similar assay and showed dramatic anti-inflammatory activity. The assay is a streptococcal cell wall (SCW) induced reactivation arthritis assay. Female Lewis rats were injected intra-articularly with 10 µL of 100 p fraction peptidoglycan polysaccharide (PG-PS) suspended in phosphate buffered saline (PBS). The contralateral joints were injected with PBS as control. Systemic challenge with 100 µg of PG-PS was given via the tail vein 21 days after the initial inoculation. The animals were dosed orally three times a day with pregabalin (3, 10, and 30 mg/kg) on a 12-hour cycle for 72 hours. The first dose was given 1 hour before the systemic challenge.

Systemic challenge on Day 21 of previously sensitized animals with SCW resulted in acute swelling in the sensitized ankle. The volume of the ankles increased by about 0.5 mL within 72 hours. Pregabalin at 10 and 30 mg/kg dose dependently attenuated the increase in edema up to 40% during the 72-hour observation period. The results are present in Table 1.

TABLE 1

Effect of Pregabalin on Ankle Swelling
(Days 0-20 were sensitization period)

	Swelling (delta edema, mL)				Pregabalin oral (mg/kg)
	Day 21 PG-PS Challenge	Day 22	Day 23	Day 24	
	0	0.20	0.45	0.50	0 (n = 6)
	0	0.12	0.38	0.50	3.0 (n = 6)
	0	0.04	0.25	0.31	10.0 (n = 4)
	0	0.06	0.20	0.21	30.0 (n = 6)

The foregoing assay establishes that GABA analogs such as gabapentin and pregabalin are effective anti-inflammatory agents and cause a reduction in swelling of the type encountered in patients suffering from arthritis.

EXAMPLE 3

Pregabalin (which is an S-isomer, and is also known as CI-1008, and as S-(+)-3-IBG) was also evaluated in the following anti-inflammatory test, along with the corresponding R-isomer, (R)-3-(aminomethyl)-5-methyl-hexanoic acid (also referred to as R-(-)-3-IBG). Acute experimental arthritis was induced in rats by injection of kaolin and carrageenan into the knee joint. The inflammatory agent, carrageenan, causes plasma extravasation and edema following the release of neuropeptides and other inflammatory mediators into the joint cavity. Concomitant with the injury to the joint tissue, both peripheral and central sensitization occurs, which is manifested in the awake rat as hyperalgesia, which can be easily quantified by measuring a reduction in paw withdrawal latencies to a radiant heat source. Both pregabalin and its R-stereoisomer (R-(-)-3-IBG) were administered before inflammation was induced, and after the inflammation was developed.

Thirty-six male Sprague-Dawley rats (235-380 g) were anesthetized with sodium pentobarbital (Nembutal; 50 mg/kg^{-1} i.p.). A microdialysis fiber (200 μm o.d., 45000 MW Cut-off, Hospal AN69) was coated with epoxy resin, except for a 2 mm section. A small midline incision was made in the back at the level of the last rib. The muscle was then removed from around the T_{12} vertebra and a hole drilled in both lateral aspects. The microdialysis fiber was then passed transversely through the dorsal horn of the spinal cord between lumbar segments L_4-L_6 so that the permeable 2 mm of the fiber lay in the dorsal horn. The microdialysis fiber was connected to PE_{20} tubing (Becton and Dickson) which was then tunneled under the skin to the nape of the neck. The fiber was stabilized with dental cement. Artificial cerebrospinal fluid (aCSF) was pumped through the

tubing at a rate of 5 μL/min for 1 hour before the PE_{20} was sealed and the animals allowed to recover.

As a measure of thermal hyperalgesia, animals were tested for paw withdrawal to radiant heat. On the day following fiber placement, animals were housed in small lucite cubicles on an elevated glass plate. Radiant heat was applied to the plantar surface of the heel of the hindpaw until the rat lifted the paw. The time at which this occurred was considered the paw withdrawal latency (PWL). Both paws were tested independently at 5-minute intervals, for a total of 5 trials. A mean of these five readings was used as the PWL. In pre-treatment rats, PWL was measured before administration of any GABA analogs (baseline) and after the GABA analog had been infused for 1.5 hours, at which time kaolin and carrageenan was injected into the knee joint. PWL was measured for a final time 4 hours after arthritis induction. In the post-treatment group, the animals were tested before induction of arthritis in the knee joint (control), 4-hours post-induction, and 1.5 hours after of drug infusion, i.e. 5.5 hours after arthritis induction. A decrease in the PWL to radiant heat in an animal with knee joint inflammation is indicative of secondary hyperalgesia.

The circumference of the knee joint was also measured before injection of kaolin and carrageenan (control) using a flexible tape measure. The extent of guarding of the hindpaw was also noted after arthritis was induced. To quantify these changes, the animals were graded by a subjective pain rating scale (0-5), where: 0 is normal; 1 is curling of the toes; 2 is eversion of the paw; 3 is partial weight bearing; 4 is non-weight bearing and guarding; and 5 is avoidance of any contact with the hindlimb.

Induction of Arthritis

Rats were anesthetized briefly with sodium methohexital (Brevital; 60 mg/kg^{-1} i.p.) after the control behavioral test (post-treatment group) or after infusion of the drug (pre-treatment group). The knee joint was then injected with 3% kaolin and 3% carrageenan suspended in sterile saline (0.1 mL; pH 7.4). The knee joint was then flexed manually until the rat awoke (approximately 5 minutes).

Administration of GABA Analogs

All GABA analogs were dissolved in an artificial cerebral spinal fluid solution (aCSF) (pH 7.4, adjusted by bubbling with 95% CO_2/5% O_2) and infused through the spinal cord at 5 $\mu L/min^{-1}$. The animals received either pregabalin, R-(-)-3-IBG, or aCSF. In the post-treatment group, the GABA analogs were infused at concentrations of 0.1, 0.9, and 10 mg/mL. In contrast, the pre-treatment group received a single dose of 10 mg/mL.

Statistical Analysis

The data was normally distributed. Statistical analyses were carried out using unpaired t-tests for comparison of differences between treatment groups at the same timepoint. Paired t-tests were used to compare before and after treatment within the same group. A P value of less than 0.05 was used to indicate significance. Data are expressed as means ±s.e.m. Tests were carried out using Statistica (Jandel Corporation).

Results

Effect of Pregabalin and its R-Isomer Infused Into the Spinal Cord Before the Development of Acute Arthritis

Infusion of 10 mg/mL of pregabalin, its R-isomer, or aCSF into the dorsal horn of the spinal cord alone did not change PWL in the thermal hyperalgesia test when compared to baseline values. The PWL of the rats treated with aCSF before the induction of inflammation was significantly reduced at 4 hours after injection of kaolin and carrageenan ($P < 0.01$, paired t-test), when compared to the value recorded immediately before injection. There was also a significant difference ($P < 0.05$, unpaired t-test) between the injected limb and the uninjected limb at this time.

However, in the rats infused with a concentration of 10 mg/mL pregabalin or its R-isomer through the spinal cord for 1.5 hours before the injection of kaolin and carrageenan into the knee joint, no secondary thermal hyperalgesia was observed 4-hours post-injection (Figure 1, top panel). No significant difference

was observed between the PWL value recorded 4 hours after inflammation and that recorded prior to injection of kaolin and carrageenan, nor between the inflamed limb and the uninflamed limb 4 hours after injection of kaolin and carrageenan.

Infusion of pregabalin or its R-isomer into the spinal cord for 1.5 hours before the induction of arthritis also significantly reduced ($P < 0.05$; unpaired t-test) the amount of swelling typical after injection of kaolin and carrageenan into the knee joint by approximately 30%, when compared to rats in which aCSF was infused (Figure 1, middle panel). Further, pre-treatment with pregabalin or its R-isomer prevented the development of abnormal paw posture indicative of spontaneous pain (Figure 1, bottom panel).

Effect of Pregabalin and its R-isomer Infused Into the Spinal Cord After the Development of Acute Arthritis

Four hours after the induction of acute inflammation of the knee joint, there was a decrease in the PWL to radiant heat of the ipsilateral footpad, when compared to the control value, in all animals tested ($n = 30$), indicating the presence of secondary hyperalgesia (Figure 2). This decrease was significant (paired t-test, $p < 0.01$). Four hours after inflammation of the knee joint, there was a significant increase in knee joint circumference compared to the measurement recorded immediately before injection of kaolin and carrageenan ($P < 0.05$, paired t-test; Figure 3). After inflammation, there was also a change in the rats' posture (decreased weight bearing upon the swollen limb, and curling of the toes) reflected by the increased spontaneous pain rating score given to the rats (Figure 4, hollow bars).

The infusion of 0.9 mg/mL pregabalin or its R-isomer into the dorsal horn of the spinal cord reduced the thermal hyperalgesia at 5.5 hours (Figure 2, upper panel). Although the PWL recorded after infusion of either drug was significantly different from that recorded 4 hours after inflammation, it was still significantly less than the control value. Pregabalin was more effective in reducing thermal hyperalgesia than its R-isomer. Infusion of a higher dose, 10 mg/mL, of pregabalin or its R-isomer, after inflammation of the knee joint, resulted in a return of the

PWL to the control value (Figure 2, lower panel). In contrast, infusion of aCSF into the dorsal horn did not reduce the thermal hyperalgesia; the PWL at 4 hours after inflammation and after aCSF infusion were not significantly different.

The spontaneous pain was also reduced by infusion of both doses of pregabalin and its R-isomer. After infusion of either isomer of the drug, the paw posture was almost normal, whereas after infusion of aCSF, curling of the toes and eversion of the paw were observed.

The results from these studies show that injection of kaolin and carrageenan into the knee joint of the rat results in an acute arthritis which is characterized by secondary thermal hyperalgesia, swelling of the knee joint, and spontaneous pain. Infusion of pregabalin and R-(-)-3-IBG into the dorsal horn of the spinal cord for 1.5 hours before the injection of kaolin and carrageenan reduced the amount of swelling observed, and blocked the secondary hyperalgesia and spontaneous pain. The GABA analogs are thus useful to treat inflammatory diseases, especially arthritis.

EXAMPLE 4

Gabapentin, another GABA analog, was evaluated in a similar assay and shown to be effective in both preventing and reversing the affects of kaolin/carrageenan knee joint inflammation, secondary heat hyperalgesia and spontaneous pain-related behaviors.

Methods

Thirty animals in two experimental groups were treated (1) prior to, and (2) after induction of experimental arthritis. Inflammation was induced within the knee joint by injection of kaolin/carrageenan. Gabapentin or aCSF was administered through a microdialysis fiber positioned in the dorsal horn for spinal treatment, or subcutaneously in the nape of the neck for systemic release. All experiments were carried out by an observer blind to the drug treatment.

Placement of microdialysis fibers. Sprague-Dawley rats (220-270 g) were anesthetized with sodium pentobarbital (nembutal, 50 mg/kg, i.p.). A

microdialysis fiber (200 μm o.d., 45000 MW Cut-off, Hospal AN69) was coated with epoxy resin, except for a 2 mm section. In 24 animals, the microdialysis fiber was placed in the dorsal horn. A small midline incision was made in the skin over the L_1 vertebral level. The L_1 vertebra was cleared of muscle and a hole drilled in both sides of the lamina. The microdialysis fiber was then passed through the holes in the vertebrae and transversely through the dorsal horn of the spinal cord. The microdialysis fiber lay between L_4-L_6 segments with the permeable 2 mm of the fiber in the dorsal horn. The microdialysis fiber was connected to PE_{20} tubing (Becton Dickinson) which was tunneled under the skin to the nape of the neck. The connecting joint between the microdialysis fiber and PE_{20} tubing was stabilized with dental cement. The aCSF was pumped through the tubing at a rate of 5 μL/min for 1 hour before the PE_{20} tubing was sealed, and the animal was allowed to recover for 24 hours. Once the rats were awake, they were examined for motor deficits; any rat which had motor deficits was excluded from the study. As a systemic control for drug administration in another 6 rats, the microdialysis fiber was implanted in the subcutaneous tissue at the nape of the neck.

Behavior testing and assessment of arthritis. The PWL to noxious radiant heat was tested as a measure of thermal hyperalgesia. A decrease in the PWL in animals with knee joint inflammation was interpreted as indicative of secondary hyperalgesia. Since the radiant heat stimulus is applied to the plantar surface of the hindpaw at quite some distance from the inflamed knee joint, the measure reported represents secondary heat hyperalgesia.

On the day following fiber placement, animals were housed in small lucite cubicles on an elevated glass plate. Radiant heat was applied to the plantar surface of the hindpaw until the rat lifted the paw. The time at which this occurred was considered the PWL. Both paws were tested independently at 5-minute intervals for a total of five trials. A mean of these five readings was used as the PWL for each time points. In pretreatment rats (n = 12), PWL was measured before administration of any drugs (baseline), after the drug had been infused for 1.5 hours (post-drug), and 4 hours after arthritis. In the post-treatment group

(n = 18), the animals were tested before induction of arthritis in the knee joint (baseline), 4 hours after induction of arthritis, and 1.5 hours after drug infusion, i.e., 5.5 hours after arthritis induction.

The pain-related behavior, the extent of guarding of the hindpaw of the arthritis limb, was scored by two independent observers. To quantify these changes, the animals were graded by a subjective pain rating scale (0-5) where: 0 is normal, 1 is curling of the toes, 2 is eversion of the paw, 3 is partial weight bearing, 4 is non-weight bearing and guarding, and 5 is avoidance of any contact with the hindpaw.

The circumference of the knee joint was also measured using a flexible tape measure before induction of arthritis (baseline), 4 hours after induction of arthritis (pretreatment and posttreatment group), and 1.5 hours after drug infusion in the posttreatment group (5.5 hours after induction of arthritis).

Induction of arthritis. Rats were anesthetized briefly with methohexital sodium (Brevital sodium, 60 mg/kg i.p.) after baseline behavior test (post-treatment group) or after infusion of the drug (pre-treatment group). The knee joint was then injected with 0.1 mL of 3% kaolin and 3% carrageenan suspended in sterile saline, and was flexed manually until the rat awoke (approx. 5-10 min.).

Administration of drug. The animal received either gabapentin or aCSF as a control. The gabapentin was dissolved in aCSF. Both gabapentin and aCSF were infused through the microdialysis fiber at a rate of 5 μL/minute. The pH of the gabapentin solution and aCSF were adjusted by bubbling with 95% CO_2/5% O_2 (about 7.4) before using.

The single dose of 10 mg/mL of gabapentin was used for the study.

Statistical analysis. The results for each group were expressed as the average percent change from baseline ± the standard error of the mean (s.e.m.). Paired t-tests were used to compare each animal's test responses to its own baseline ($P < 0.01$).

Results

Baseline measures. The baseline PWL, spontaneous behavior, and knee joint circumference of all rats used in these studies were measured prior to infusion of the drug or vehicle through the spinal cord or subcutaneously (Table 2). The mean PWL and knee joint circumference were 10.52 ± 0.39 sec and 5.26 ± 0.03 cm, respectively. No spontaneous pain-related behaviors were noted and a score of zero given.

Consequent changes with joint inflammation. In Table 2, the expected outcome in arthritic animals for all measures is presented. The data includes the combined measures for the aCSF arthritic control animals from both treatment groups. In the aCSF-treated arthritic control rats ($n = 12$), 4 hours after injection of kaolin and carrageenan, the PWL to noxious radiant heat decreased to 76% of baseline value. This decrease was significant (paired t-test, $p < 0.01$) and indicated the presence of secondary hyperalgesia.

In arthritic animals, there was a significant change in the hindpaw posture of the rat, indicative of spontaneous ongoing pain-related behavior. These postural changes, representing spontaneous ongoing pain-related behavior, were represented by a score of 1.25 ± 0.13 ($p < 0.01$). A significant 14% increase in knee joint circumference is noted compared to the baseline (paired t-test, $p < 0.01$).

TABLE 2

Non-arthritic Vs. Arthritic Animals

	PWL (sec.)	PWL (% of baseline)	Behavior Score	Circumference (cm)	Circumference (% of baseline)
Baseline	11.47 ± 0.56	100	0	5.18 ± 0.04	100
Arthritis (4 h)	8.66 ± 0.56*	76.42 ± 3.10*	1.25 ± 0.13*	5.92 + 0.09*	114.38 ± 1.86*

* $p < 0.01$.

The effect of gabapentin infusion directly into the spinal cord before knee joint inflammation. Gabapentin was effective in preventing the development of secondary hyperalgesia responses to the applied radiant heat. Gabapentin or aCSF were infused through the microdialysis fiber into the spinal cord before the knee joint was injected with kaolin and carrageenan. After 1.5 hours of spinal drug infusion, there were no significant changes of the PWL to the radiant heat compared to the baseline (Table 3). Four hours after injection of the knee joint with kaolin and carrageenan, the PWL response to radiant heat and the posture of the hindpaw with arthritis were not significantly changed from non-arthritic baseline. In contrast, the aCSF-treated animals had a significant reduction in their PWL responses, and demonstrated significant spontaneous pain-related behaviors. The circumference of the inflamed joint was increased significantly 4 hours after arthritis, similar to the aCSF arthritic control rats. Thus, gabapentin was highly effective in preventing the development of secondary heat hyperalgesia and measures of spontaneous pain-related behaviors.

TABLE 3

Effects of Gabapentin Administered Prior to Inflammation

Groups	Baseline (% of control)	PWL (1.5 h after drug infusion)	PWL (4 h after joint injection)	Behavior Score (4 h after joint inspection)	Circumference (4 h after joint injection)
Gabapentin (n = 6)	100	105.18 ± 4.56	100.03 ± 4.37	0.67 ± 0.20	114.20 ± 1.53*
aCSF (n = 6)	100	93.12 ± 6.31	74.47 ± 3.44*	1.33 ± 0.2*	114.87 ± 1.74*

* $p < 0.01$.

Effect of gabapentin infusion into the spinal cord or subcutaneously after knee joint inflammation. Post-treatment of arthritic animals with gabapentin reversed the secondary heat hyperalgesia and spontaneous pain-related behaviors when administered spinally. Two groups of animals received gabapentin in post-treatment studies (Table 4). One group of rats was infused with the drug through a microdialysis fiber implanted directly into the spinal cord; the other group received gabapentin systemically through a microdialysis fiber implanted subcutaneously at the nape of the neck.

Four hours after injection of kaolin and carrageenan, all animals displayed reduced PWL responses and spontaneous pain-related behaviors. In the group infused with gabapentin spinally, the PWL significantly decreased to about 81% of baseline measurements (paired t-test, $p < 0.01$). By 1.5 hours after spinal gabapentin infusion, the PWL measurements returned back to the baseline, and the toes became almost flat.

TABLE 4

Effects of Gabapentin Administered After Inflammation

Groups	PWL or Circumference (% of control)	PWL (after 4 h arthritis)	PWL (after 5.5 h arthritis)	Behavior Score (after 5.5 h arthritis)	Circumference (after 5.5 h arthritis)
Gabapentin (spinal cord) (n = 6)	100	80.71 ± 3.23*	100.85 ± 10.63	0.50 ± 0.20	122.22 ± 2.32*
Gabapentin (subcutaneous) (n = 6)	100	85.05 ± 3.68*	81.89 ± 4.43*	1.17 ± 0.29*	120.66 ± 3.59*
aCSF (spinal cord) (n = 6)	100	78.37 ± 5.37*	78.57 ± 4.38*	1.17 ± 0.28*	113.89 ± 3.49*

* $p < 0.01$.

In the group which was infused with gabapentin subcutaneously, the PWL to noxious radiant heat significantly decreased by 15% from baseline measurements 4 hours after joint injection, and after 1.5 hours drug infusion, the

PWL continued to decrease to 82% of the baseline value, similar to aCSF control arthritic rats. Both the pain-related behavior score and the circumference of the inflamed joint increased significantly after 4 hours arthritis and 1.5 hours drug infusion (5.5 h post) for all groups.

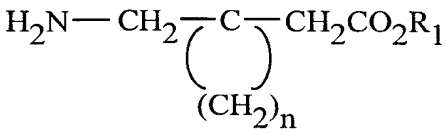
The foregoing study establishes that GABA analogs such as gabapentin are effective in both preventing and reversing the affects of kaolin/carrageenan knee joint inflammation on secondary heat hyperalgesia and spontaneous pain-related behaviors. In both treatment groups, the significant finding was the ability of gabapentin to retain (or return) the PWL latency scores to baseline. Its effectiveness in reducing the hyperalgesia and pain-related behavior after the arthritis is fully developed in this model indicates that gabapentin and similar GABA analogs will have clinically useful effects in clinical inflammatory conditions.

CLAIMS

What is claimed is:

1. A method for preventing and treating inflammatory diseases comprising administering to a subject in need of treatment an anti-inflammatory amount of a GABA analog.

2. A method according to Claim 1 employing a compound of Formula I



I

wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

3. The method according to Claim 2 employing gabapentin.

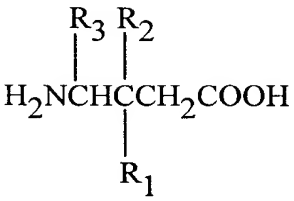
4. A method according to Claim 2 employing a compound of Formula I wherein the cyclic ring is substituted with one or two groups selected from methyl and ethyl.

5. The method according to Claim 4 employing (1-aminomethyl-3-methylcyclohexyl) acetic acid.

6. The method according to Claim 4 employing (1-aminomethyl-3-methylcyclopentyl) acetic acid.

7. The method according to Claim 4 employing (1-aminomethyl-3,4-dimethylcyclopentyl) acetic acid.

8. A method according to Claim 1 employing a compound of Formula II



II

wherein R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl, and the pharmaceutically acceptable salts thereof.

9. The method according to Claim 8 employing pregabalin.

10. The method according to Claim 8 employing R-(3)-(aminomethyl)-5-methyl-hexanoic acid.

11. The method according to Claim 8 employing 3-(1-aminoethyl)-5-methyl-hexanoic acid.

FIG-1A

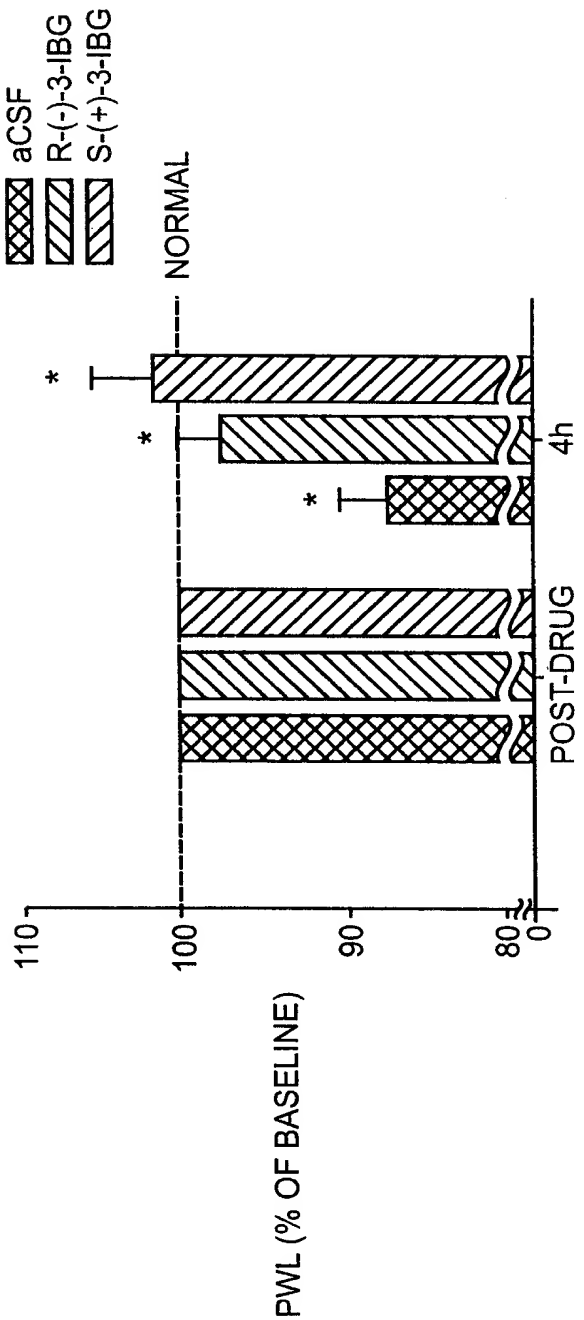

aCSF
R-(-)-3-IBG
S-(+)-3-IBG
NORMAL
*
*
*
4h
POST-DRUG
110
100
90
80
0
PWL (% OF BASELINE)

FIG-1B

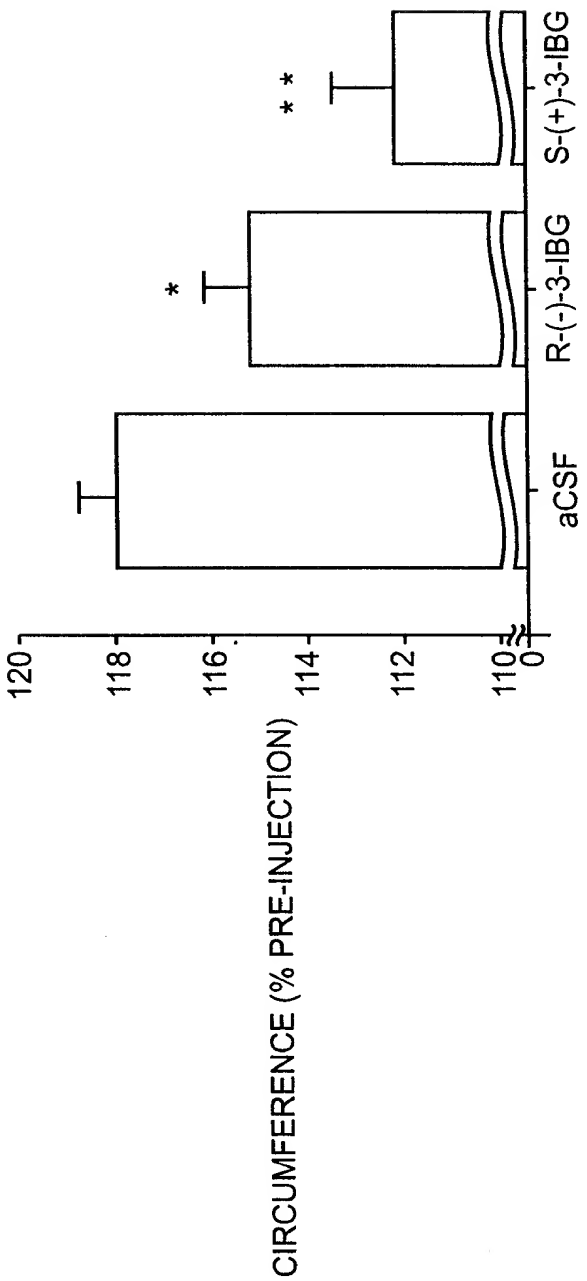

CIRCUMFERENCE (% PRE-INJECTION)
120
118
116
114
112
110
0
*
* *
aCSF
R-(-)-3-IBG
S-(+)-3-IBG

FIG-1C

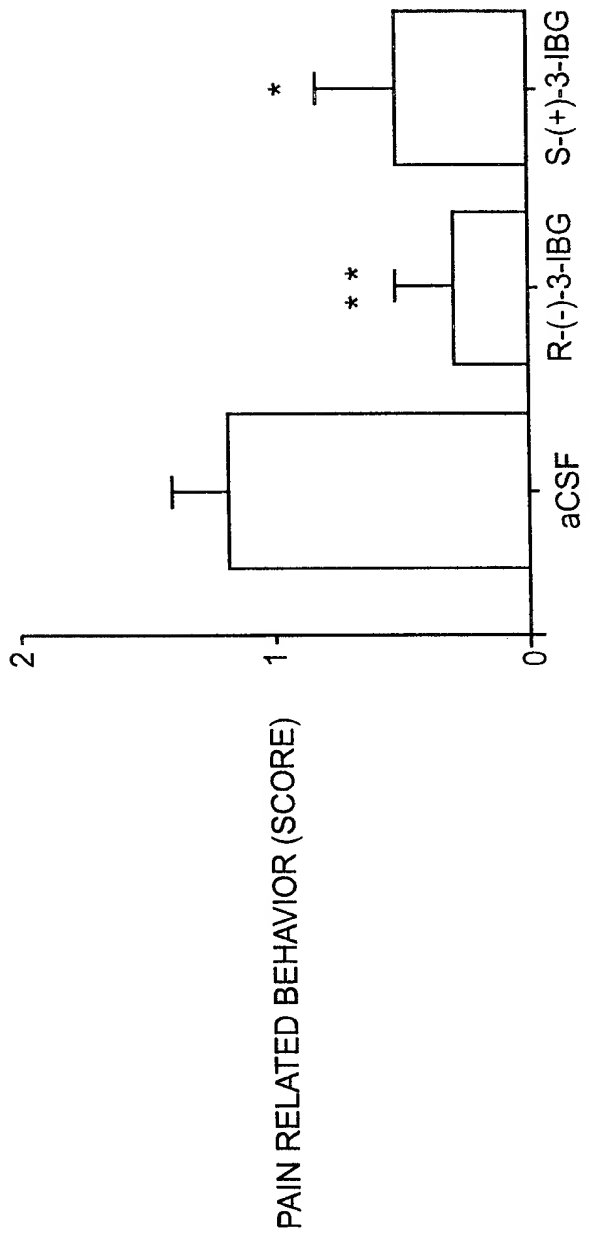


FIG-2A

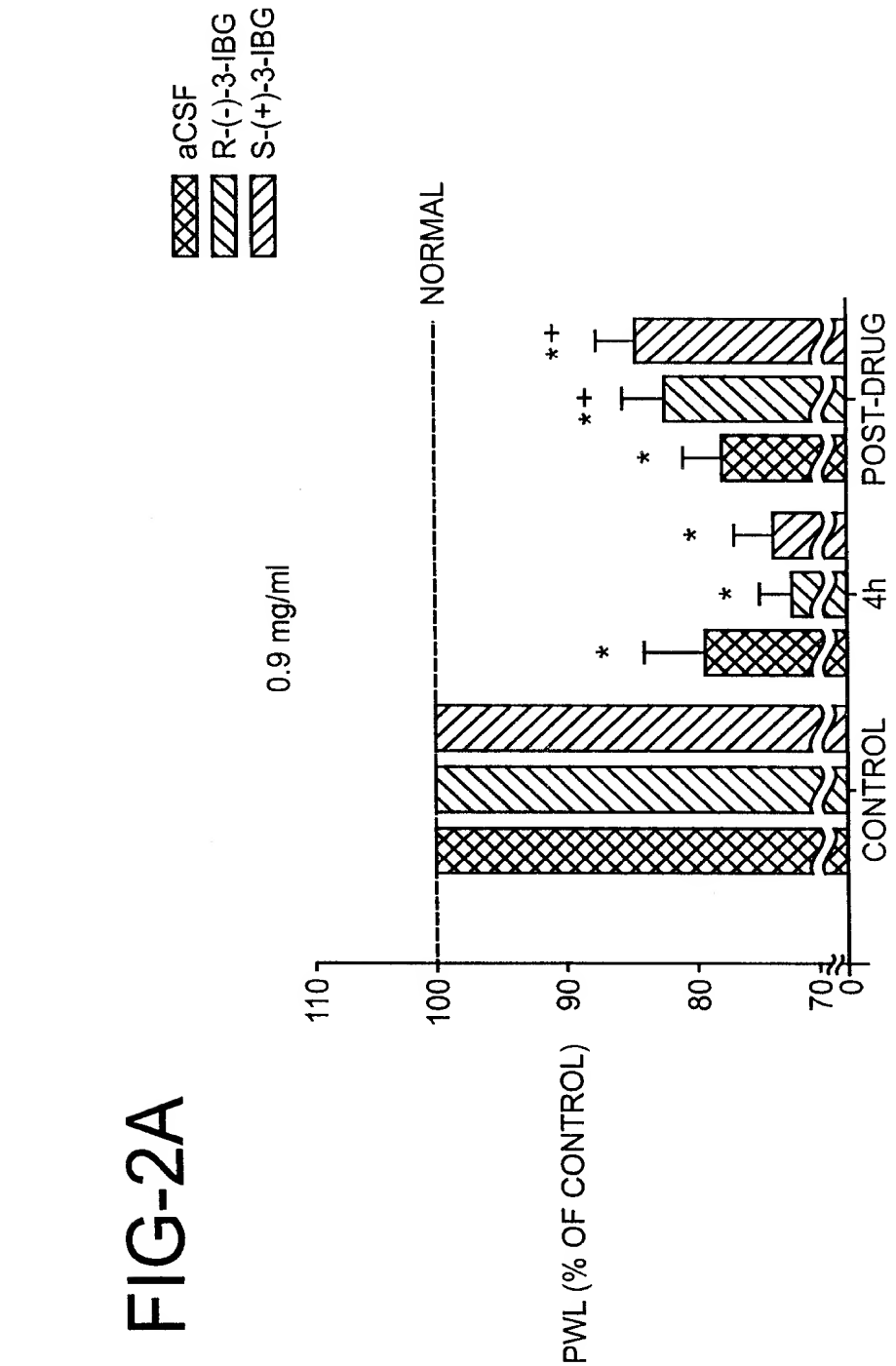

aCSF
R-(-)-3-IBG
S-(+)-3-IBG
0.9 mg/ml
NORMAL
CONTROL
4h
POST-DRUG
PWL (% OF CONTROL)
110
100
90
80
70
0
*
*
*
*
*+
*+

FIG-2B

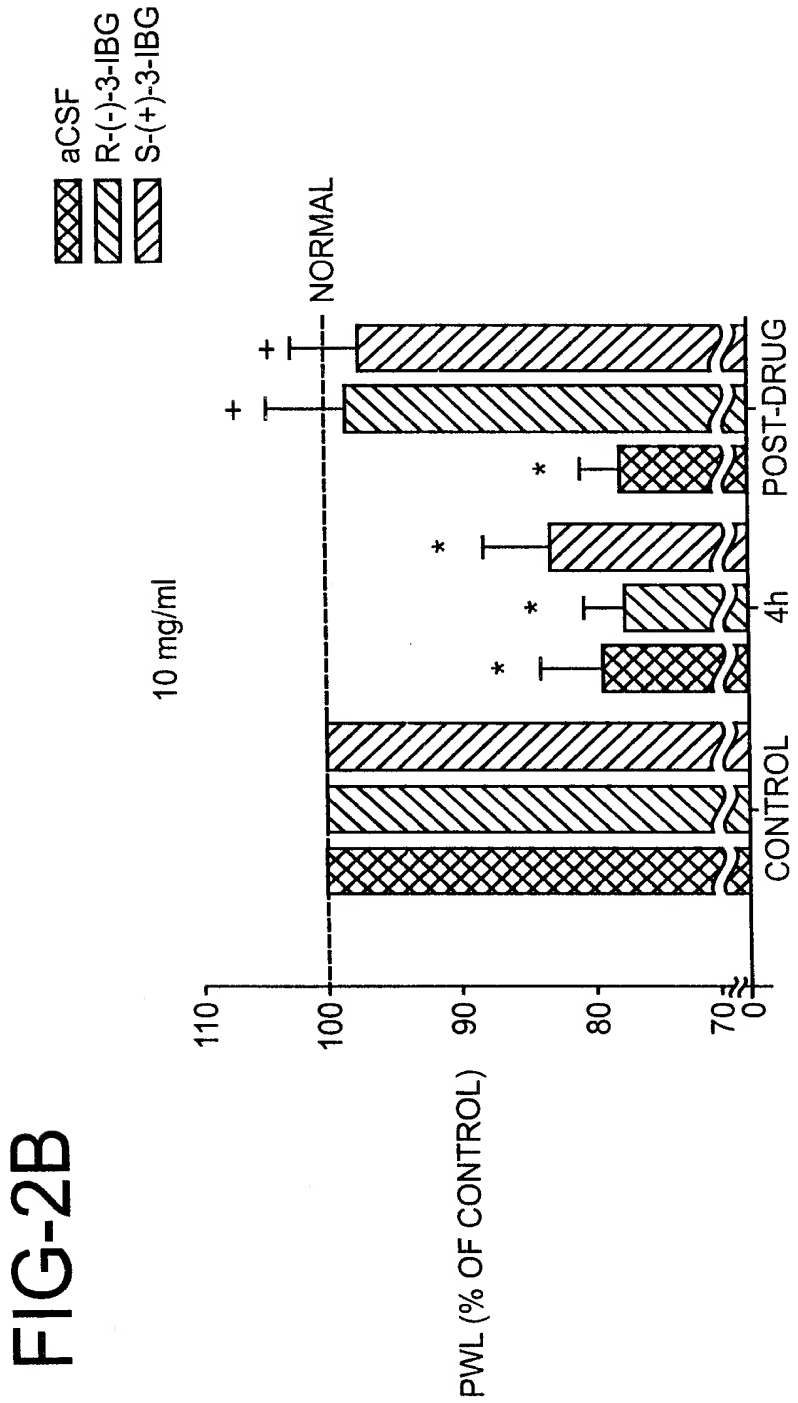
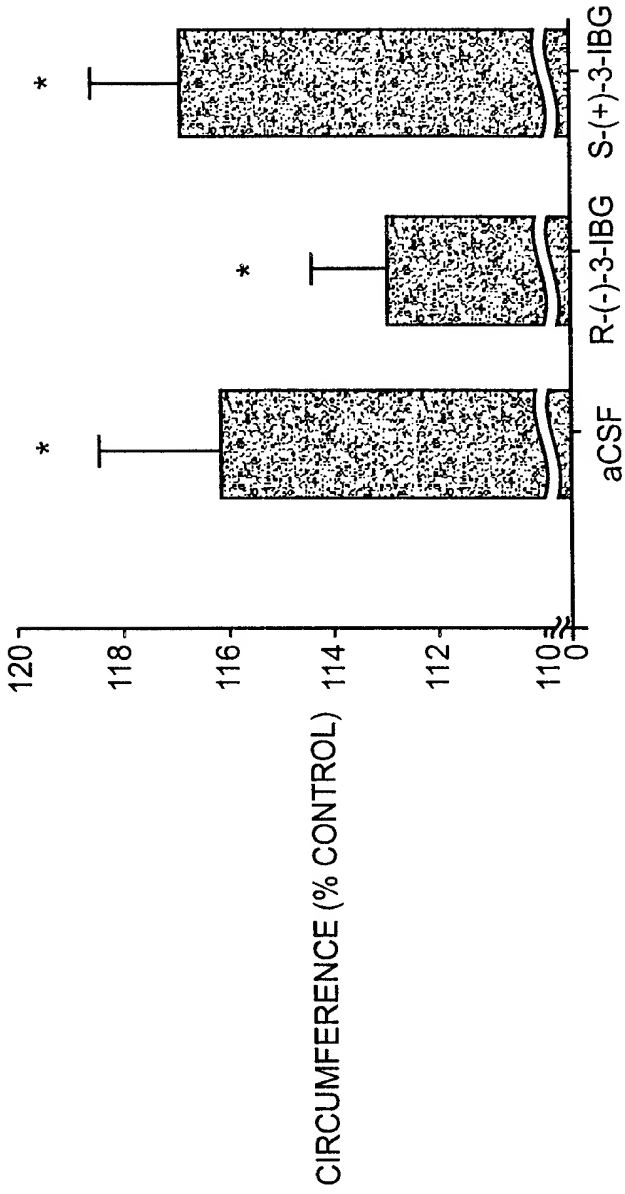

aCSF
R-(-)-3-IBG
S-(+)-3-IBG
10 mg/ml
NORMAL
CONTROL
4h
POST-DRUG
PWL (% OF CONTROL)
110
100
90
80
70
0
+
*

FIG-3A


0.9 mg/ml
CIRCUMFERENCE (% CONTROL)
120
118
116
114
112
110
0
aCSF
R-(-)-3-IBG
S-(+)-3-IBG
*
*
*

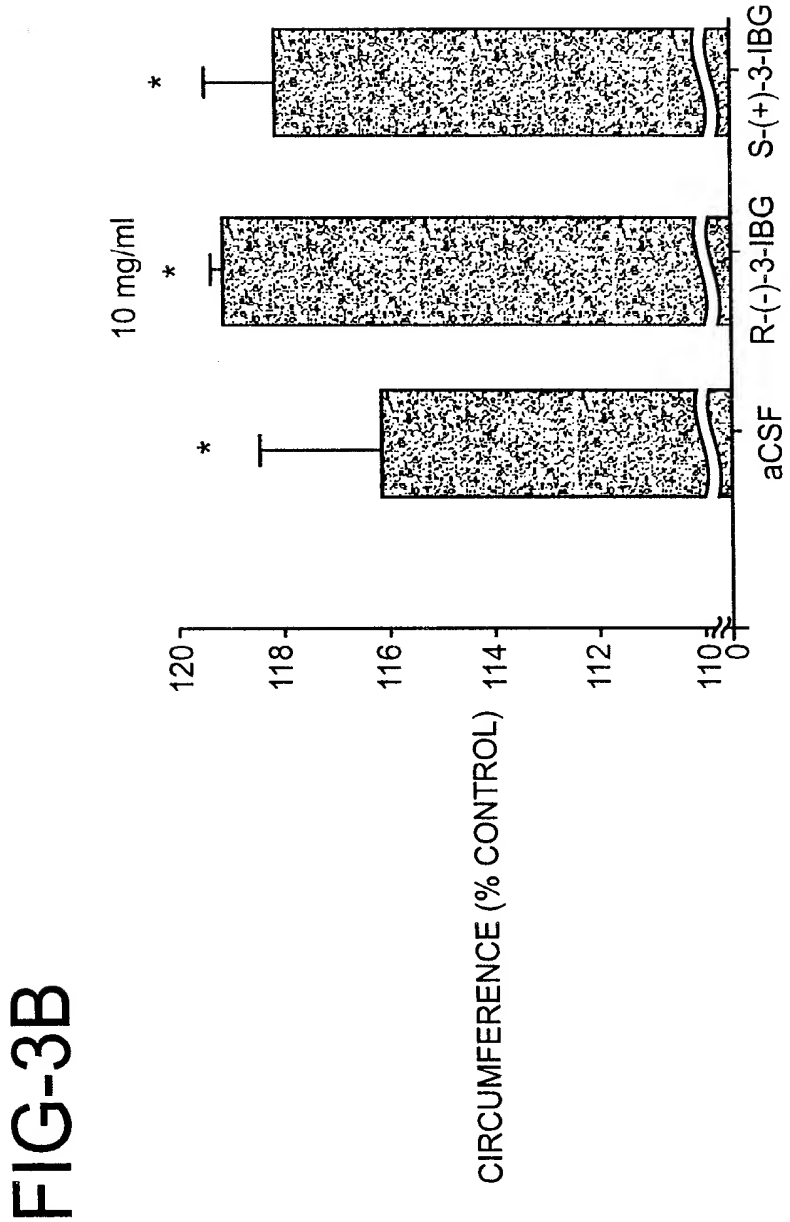

10 mg/ml
*
*
*
aCSF
R-(-)-3-IBG
S-(+)-3-IBG
CIRCUMFERENCE (% CONTROL)
120
118
116
114
112
110
0

FIG-3B

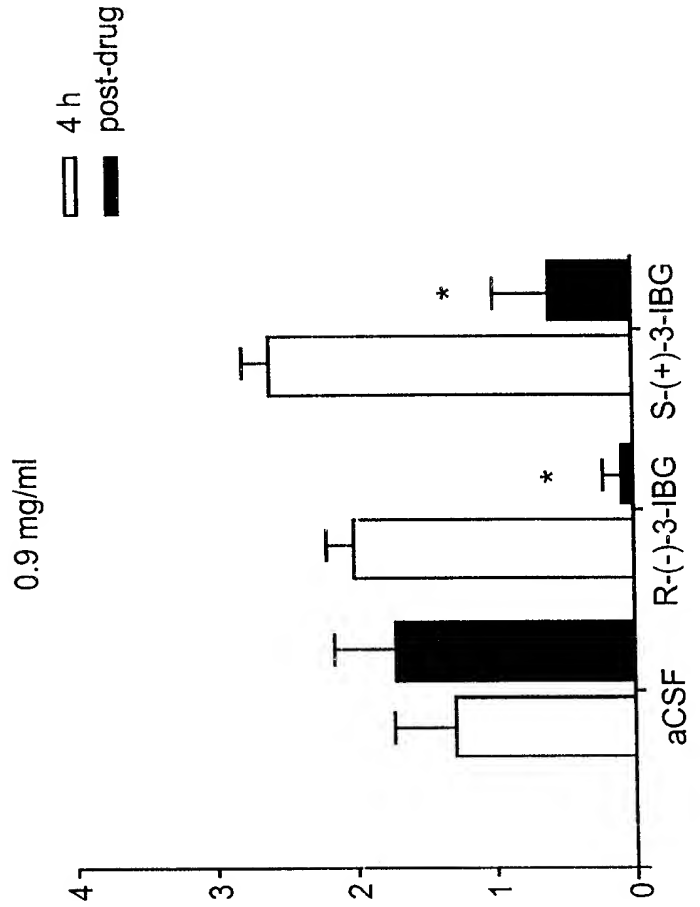


FIG-4A

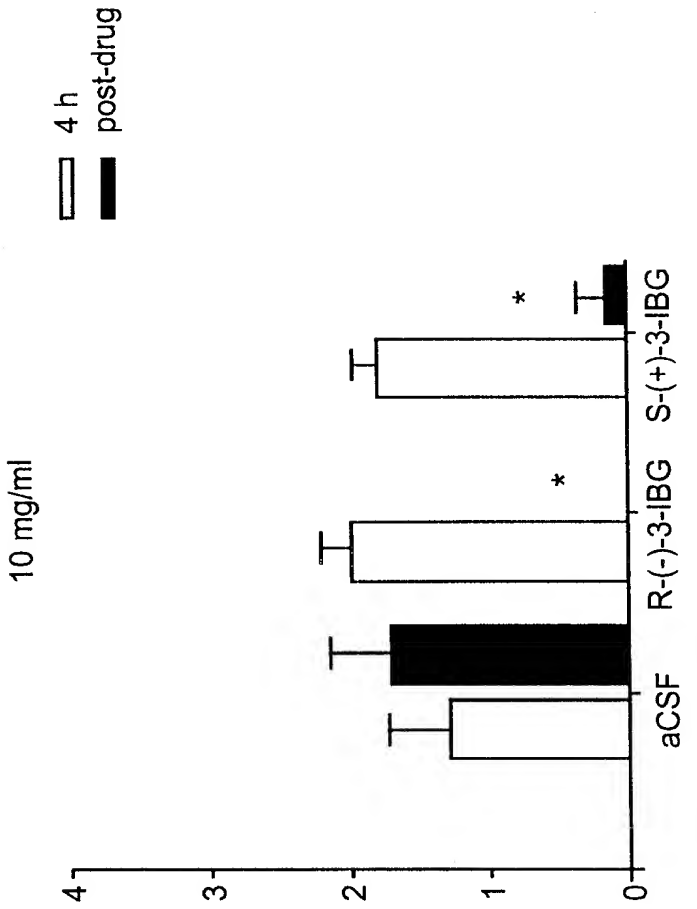


FIG-4B

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 98/13107

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 8514 Derwent Publications Ltd., London, GB; Class B05, AN 85-084635 XP002082265 & JP 60 036413 A (NAGAI K) , 25 February 1985 see abstract	1
Y	see the whole document	2-11
P,X	WO 98 17627 A (BRYANS JUSTIN STEPHEN ;HORWELL DAVID CHRISTOPHER (GB); KNEEN CLARE) 30 April 1998 * p.1, l.18; claim 1 *	1
P,Y	WO 98 03167 A (SINGH LAKHBIR ;WARNER LAMBERT CO (US)) 29 January 1998 see claims 1-4	8-11

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1998	05/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Uiber, P

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 98/13107

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document. with indication,where appropriate. of the relevant passages	Relevant to claim No.
Y	US 4 024 175 A (SATZINGER GERHARD ET AL) 17 May 1977 cited in the application see claims 1-11	2-7
Y	US 5 563 175 A (SILVERMAN RICHARD B ET AL) 8 October 1996 see claim 1	8-11

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/13107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9817627 A	30-04-1998	AU 4669797 A	15-05-1998
WO 9803167 A	29-01-1998	AU 3602497 A	10-02-1998
US 4024175 A	17-05-1977	DE 2460891 A	01-07-1976
		AT 340892 B	10-01-1978
		AT 975075 A	15-05-1977
		AU 8774175 A	23-06-1977
		BE 836835 A	18-06-1976
		CA 1052811 A	17-04-1979
		CH 612665 A	15-08-1979
		CH 612666 A	15-08-1979
		CH 612664 A	15-08-1979
		DE 2543821 A	14-04-1977
		DK 581475 A,B,	22-01-1976
		FI 753613 A,B,	22-06-1976
		FR 2294697 A	16-07-1976
		GB 1465229 A	23-02-1977
		IE 42382 B	30-07-1980
		JP 941538 C	20-02-1979
		JP 51088940 A	04-08-1976
		JP 53024064 B	18-07-1978
		LU 74058 A	20-07-1976
		NL 7514900 A,B,	23-06-1976
		SE 423385 B	03-05-1982
		SE 7514442 A	22-06-1976
		US 4087544 A	02-05-1978
US 5563175 A	08-10-1996	MX 9302970 A	31-05-1994
		US 5684189 A	04-11-1997
		US 5608090 A	04-03-1997
		US 5599973 A	04-02-1997
		US 5710304 A	20-01-1998
		AU 677008 B	10-04-1997
		AU 4379493 A	13-12-1993
		CA 2134674 A	25-11-1993
		CZ 9402849 A	15-03-1995
		EP 0641330 A	08-03-1995
		FI 945426 A	18-11-1994
		HU 71522 A	28-12-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

In ational Application No
PCT/US 98/13107

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5563175 A		JP 7508288 T	14-09-1995
		NO 944370 A	21-11-1994
		NZ 253459 A	24-03-1997
		SG 48288 A	17-04-1998
		SK 139594 A	10-05-1995
		WO 9323383 A	25-11-1993
		AU 9137091 A	25-06-1992
		MX 9102241 A	31-01-1994
		WO 9209560 A	11-06-1992

ASSIGNMENT

As a below-named inventor, I hereby declare that:

My post office address is as stated below under my signature and I am named as an inventor of the inventions or discoveries (herein INVENTIONS) as described in the patent application (herein APPLICATION) identified below. In view of valuable consideration, receipt thereof is hereby acknowledged, I do hereby assign and transfer unto **WARNER-LAMBERT COMPANY** a corporation of the State of Delaware having a place of business at ANN ARBOR, MICHIGAN, its successors and assigns, my entire interest in and the full exclusive right to the INVENTIONS, the APPLICATION, and all related applications (including provisionals, divisions, reissues, continuations, and extensions thereof) and all counterparts in other countries, and any and all Letters Patent (and certificates of invention or similar certificates) (herein PATENTS) which may be granted based upon the INVENTIONS or the APPLICATION or related applications or counterparts in other countries; said transfer and assignment being applicable throughout the world. I hereby authorize and request officials of patent offices in any and all countries of the world to issue any and all of the PATENTS, when granted, to WARNER-LAMBERT COMPANY, its successors and assigns, as the assignee of my entire right, title, and interest in and to the same. I agree that I will communicate to WARNER-LAMBERT COMPANY, or its representatives, any facts known to me respecting the invention; testify in any legal proceedings; sign all lawful papers; execute all provisional, divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of the PATENTS to be issued to WARNER-LAMBERT COMPANY; make all rightful oaths; and generally do everything possible to aid WARNER-LAMBERT COMPANY, its successors, and assigns, to obtain and enforce proper protection for the INVENTION in any and all countries throughout the world. The APPLICATION is identified herein.

Japanese Serial No. (if known): 133112/98
Filing Date (if known): May 15, 1998

Corresponding to:

United States Serial No. (if known): 60/086,269
Filing Date (if known): May 21, 1998
Execution Date(s) of Application:

Title: GABAPENTIN-CONTAINING SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME

FULL NAME OF INVENTOR : AKIRA AOMATSU

Signature of Inventor : A. Aomatsu Date 4/2/1999

Address : 34-8-302, Matsuka
Hachioji-shi, Tokyo 192-0362 JAPAN

On 2nd April, 1999, at MEGURO, TOKYO, JAPAN the above-named inventor personally appeared before me and executed the foregoing instrument and acknowledged the same to be his/her free act and deed in and for the purposes set forth in said instrument.

Kazutoshi Yamamoto
Notary Public

My Commission Expires: NOTARY

as you will see
in the attached paper

TOKYO · MEGURO NOTARY PUBLIC · JAPAN · KAZUTOSHI YAMAMOTO

Registered No. 1 2 2

NOTARIAL CERTIFICATE

This is to certify that A K I R A A O M A T S U has affixed his signature in my very presence to the foregoing document.

Dated this 2nd day of April, 1999.

NOTARY Kazutoshi Yamamoto

Kazutoshi Yamamoto

NOTARY
TOKYO LEGAL AFFAIRS BUREAU
17-5, 2chome, Kami-Osaki,
Shinagawa-ku, Tokyo,
Japan

TOKYO・MEGURO NOTARY PUBLIC・JAPAN・KAZUTOSHI YAMAMOTO
目黒公証役場

平成11年登簿第122号

認　　証

嘱託人青松晃

は、本公証人の面前で、別紙添付の書面に署名

した。

よつて、これを認証する。

平成11年4月2日、本公証人役場において

東京都品川区上大崎2－17－5

東京法務局所属

公証人 山和和敏

証　　明

上記署名は、東京法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成11年4月2日

東京法務局長 櫻井

CERTIFICATE

This is to certify that the signature affixed above has been provided by Notary, duly authorized by the Tokyo Legal Affairs Bureau and that the Official Seal appearing on the same is genuine.

Date APR. - 2. 1999

Hiroshi SAKURAI
Director of the Tokyo Legal Affairs Bureau

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: JAPAN

This public document

2. has been signed by Hiroshi SAKURAI

3. acting in the capacity of Director of the Tokyo Legal Affairs Bureau

4. bears the seal/stamp of

Certified

5. at Tokyo 6. APR. - 2. 1999

7. by the Ministry of Foreign Affairs

8. 00 - NO 007460

9. Seal/stamp:

10. Signature:

Shigekazu SAKAMATA

For the Minister for Foreign Affairs

Exhibit C

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

U.S. APPLICATION NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
09/674819	AOMATSU A	5774-01-MJA

INTERNATIONAL APPLICATION NO.
PCT/US99/10186

I.A. FILING DATE	PRIORITY DATE
10 MAY 99	21 MAY 98

CHARLES W ASHBROOK
WARNER LAMBERT COMPANY
2800 PLYMOUTH ROAD
ANN ARBOR, MI 48105

DEC 27 2000

DATE MAILED: 18 DEC 2000

NOTIFICATION OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

1. The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as ☐ a Designated Office (37 CFR 1.494), ☒ an Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is **ACCEPTED** for national patentability examination in the United States Patent and Trademark Office.

2. The United States Application Number assigned to the application is shown above and the relevant dates are:

06 NOV 2000 — 35 U.S.C. 102(e) DATE

06 NOV 2000 — DATE OF RECEIPT OF 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE "FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371(C) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

3. ☒ A request for immediate examination under 35 U.S.C. 371(f) was received on 06 NOV 2000 and the application will be examined in turn.

4. The following items have been received:
- ☒ U.S. Basic National Fee.
- ☒ Copy of the international application in:
  - ☐ a non-English language.
  - ☒ English.
- ☒ Translation of the international application into English.
- ☒ Oath or Declaration of inventors(s) for DO/EO/US.
- ☐ Copy of Article 19 amendments. ☐ Translation of Article 19 amendments into English.
  The Article 19 amendments ☐ have ☐ have not been entered.
- ☒ The International Preliminary Examination Report in English and its Annexes, if any.
- ☐ Copy of the Annexes to the International Preliminary Examination Report (IPER).
  - ☐ Translation of Annexes to the IPER into English.
  - The Annexes ☐ have ☐ have not been entered.
- ☐ Preliminary amendment(s) filed _____ and _____.
- ☒ Information Disclosure Statement(s) filed 06 NOV 2000 and _____.
- ☐ Assignment document.
- ☒ Power of Attorney and/or Change of Address.
- ☐ Substitute specification filed _____.
- ☐ Verified Statement Claiming Small Entity Status.
- ☒ Priority Document.
- ☒ Copy of the International Search Report ☒ and copies of the references cited therein.
- ☐ Other:

Applicant is reminded that any communication to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above. (37 CFR 1.5)

Paulette Kidwell, Paralegal
Telephone: 703-305-3656

FORM PCT/DO/EO/903 (December 1997)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
5774-01-MJA		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 10186	10/05/1999	15/05/1998
Applicant		
WARNER-LAMBERT COMPANY et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   GAMMA-AMINOBUTYRIC ACID DERIVATIVES CONTAINING, SOLID COMPOSITIONS AND PROCESS FOR PREPARING THE SAME

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

US006329429B1

Exhibit D

(12) **United States Patent**
Schrier et al.

(10) **Patent No.: US 6,329,429 B1**
(45) **Date of Patent: Dec. 11, 2001**

(54) **USE OF GABA ANALOGS SUCH AS GABAPENTIN IN THE MANUFACTURE OF A MEDICAMENT FOR TREATING INFLAMMATORY DISEASES**

(75) Inventors: **Denis Schrier**, Ann Arbor; **Charles Price Taylor, Jr.**, Chelsea, both of MI (US); **Karin Nanette Westlund High**, League City, TX (US)

(73) Assignee: **Warner-Lambert Company**, Morris Plains, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/403,867**

(22) PCT Filed: **Jun. 24, 1998**

(86) PCT No.: **PCT/US98/13107**

§ 371 Date: **Oct. 25, 1999**

§ 102(e) Date: **Oct. 25, 1999**

(87) PCT Pub. No.: **WO98/58641**

PCT Pub. Date: **Dec. 30, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/050,736, filed on Jun. 25, 1997.

(51) **Int. Cl.**[7] **A01N 37/12**

(52) **U.S. Cl.** **514/561**; 514/729; 560/122; 560/123; 562/504; 562/505; 562/507

(58) **Field of Search** 514/561, 729; 560/122, 123; 562/504, 505, 507

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,024,175		5/1977	Satzinger et al.	260/468 J
5,518,730	*	5/1996	Fuisz .	
5,563,175		10/1996	Silverman et al.	514/561

FOREIGN PATENT DOCUMENTS

JP60036413A	2/1985	(GB) .
98/03167	1/1998	(WO) .
98/17626	4/1998	(WO) .

* cited by examiner

Primary Examiner—Gary Geist
Assistant Examiner—Robert W. Deemie
(74) *Attorney, Agent, or Firm*—Charles W. Ashbrook; Claude F. Purchase, Jr.

(57) **ABSTRACT**

GABA analogs such as gabapentin and pregabalin are useful to prevent and treat inflammatory diseases.

10 Claims, 9 Drawing Sheets